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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/490,643	Applicant(s) Minshull et al.
	Examiner Ethan Whisenant, Ph.D. (FSA)	Group Art Unit 1655

☒ Responsive to communication(s) filed on 24 JAN 00, 10 APR 00, 14 APR 00 and 26 MAY 00 .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-30* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3-4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

SEQUENCE RULES

1. This application fails to comply with the sequence rules. See the attached notice to comply with the sequence rules. It is noted that this application is a continuation of USSN 08/650,400 wherein the applicant has complied with the sequence rules. The applicant may request to use the CRF from that application using the attached sample statement as a guide.

DRAWINGS

2. The drawings filed 24 JAN 00 have been approved by the Draftsperson under 37 CFR 1.84 or 1.152.

35 U.S.C. § 112- 2ND PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

CLAIM REJECTIONS **under 35 U.S.C. § 112- 2ND** PARAGRAPH

4. **Claims 1-18 and 20-30** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 17, 18, 20 and 27 are confusing because they contain the phrase "as necessary" in part (e). This implies that this step [i.e. step (e)] is optional in these claims. Is this the applicant's intention? It is the examiner's understanding of the invention, based on his examination of other applications in the instant application's linage, that the critical limitation present in the claims is the recursive/iterative nature of the method that makes it novel. **Please clarify.** Please note that for the evaluation of these claims against the prior art the examiner has interpreted these claims as if steps (c) and (d) must be repeated at least once.

Claim 15 is indefinite because it is unclear to which recombining step the applicant refers. Claim 1 has at least two recombining steps [i.e. steps (a) and (c)] as well as multiple optional recombining steps [i.e. step (e)]. The applicant undoubtedly intends for "at least one" of the recombining steps to be performed in the cell and this is how the claim has been interpreted for the prior art rejections which follow.

Claim 21 is vague and indefinite because it is unclear to the examiner how the limitation recited further limits the claimed method (i.e. Claim 20).

Claim 22 is awkward and therefore it is unclear the limitation the applicant intends. A vector may comprise a gene, however, a gene is not vector. Clarification and amendment are required.

35 U.S.C. § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that may form the basis for rejections set forth in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. **Claims 1-3, 5, 12-13, 17, 20-22, 25-26** are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer (OCT 1994).

Claim 1 is drawn to a method of evolving the biocatalytic activity of a cell comprising at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to catalyze a reaction of interest wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of enhancement is achieved. Stemmer teaches a method of evolving the biocatalytic activity of a cell. Specifically, Stemmer teaches the DNA shuffling of the lacZα gene from $LacZ^-$ cells to produce $LacZ^+$ cells in a method comprising the steps recited in Claim 1.

Claim 2 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to utilize a substrate as a nutrient source. Stemmer teaches this embodiment wherein they teach the DNA

shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells which utilize X-gal as a nutrient source.

Claim 3 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to catabolize a compound. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells which catabolize X-gal.

Claim 5 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to synthesize a compound of interest. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells which catabolize X-gal synthesizing a nondiffusable blue pigment.

Claim 12 is drawn to an embodiment of Claim 1, wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell (i.e. *E. coli*) whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated.

Claim 13 is drawn to an embodiment of Claim 12, wherein the *in vitro* recombining step comprises cleaving the first and second segments into fragments , mixing and denaturing said fragments followed by incubating said fragments with a polymerase under conditions wherein the denatured fragment will anneal and form a library of recombinant genes. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells wherein the at least one *in vitro* recombining step comprises cleaving the first and second segments into fragments , mixing and denaturing said fragments followed by incubating said fragments with a polymerase under conditions wherein the denatured fragment will anneal and form a library of recombinant genes.

Claim 17 is drawn to a method of evolving a gene to have the ability to catalyze a reaction of interest. This method is to comprise at least four steps. The first step of the method comprises the

recombining of at least a first and a second DNA segment from at least one gene conferring the ability to catalyze the reaction of interest wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments of step (a). This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of enhancement is achieved.

Stemmer teaches a method of evolving a gene to have the ability to catalyze a reaction of interest.. Specifically, Stemmer teaches the DNA shuffling of the lacZα gene (i.e $LacZ^-$ gene) to produce $LacZ^+$ cells in a method comprising the steps recited in Claim 17.

Claim 20 is drawn to a method of optimizing the expression of a gene product . This method is to comprise at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to produce said gene product wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers optimized expression of said gene product relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers optimized expression of said gene product relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of optimized expression is achieved.

Stemmer teaches a method of optimizing the expression of a gene product . Specifically, Stemmer teaches the DNA shuffling of the lacZα gene to produce $LacZ^+$ cells from $LacZ^-$ cells in a method comprising the steps recited in Claim 20. The expression can be said to be optimized because before shuffling the cells produced inactive LacZ, however, after DNA shuffling the expression has been optimized because active LacZ could be produced.

Claim 21 is drawn to an embodiment of Claim 20, wherein at least one gene encodes the gene product. Stemmer teaches this embodiment wherein he teaches the DNA shuffling of at least one gene (i.e. the lacZα gene) to produce $LacZ^+$ cells from $LacZ^-$ cells. The lacZα gene encode the gene product LacZ.

Claim 22 is drawn to an embodiment of Claim 20, wherein the at least one gene is a vector comprising a gene encoding the gene product. Stemmer teaches this embodiment wherein he teaches the DNA shuffling of a mixture of two 2.7 kb whole plasmids each comprising inactive LacZ genes. Following DNA shuffling and reassembly Stemmer teach that the expression of LacZ had been optimized i.e. $LacZ^+$ cells are present following transformation into *E. coli*.

Claim 25 is drawn to an embodiment of Claim 20, wherein the at least one gene is a host cell gene wherein the host cell gene does not encode the gene product. Stemmer teach this embodiment wherein he teaches that following DNA shuffling of the lacZα gene produces $LacZ^+$ cells from $LacZ^-$ cells in a method comprising the steps recited in Claim 25. The at least one gene is a host cell gene (i.e. the LacZα gene is a *E. coli* gene), however, the gene product is not expressed from the host cell gene but rather from the plasmid encoded gene.

Claim 26 is drawn to an embodiment of Claim 20, wherein optimization results in increased expression of the gene product. Stemmer teaches this embodiment wherein he teaches that following DNA shuffling of the lacZα gene $LacZ^+$ cells are produced from $LacZ^-$ cells in a method comprising the steps recited in Claim 26. The expression can be said to be increased because before shuffling the cells produced inactive LacZ, however, after DNA shuffling the expression was increased because active LacZ could be produced.

7. **Claims 1, 3-6, 12-13**, are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer (AUG 1994).

Claim 1 is drawn to a method of evolving the biocatalytic activity of a cell comprising at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to catalyze a reaction of interest wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers

enhanced ability to catalyze the reaction of interest relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of enhancement is achieved.

Stemmer teaches a method of evolving the biocatalytic activity of a cell. Specifically, Stemmer teaches the DNA shuffling of the TEM-1 β-lactamase gene, a gene which catabolizes (i.e. hydrolyzes) the antibiotic cefotaxime.

Claim 3 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to catabolize a compound. Stemmer teaches a method of evolving the biocatalytic activity of a cell. Specifically, Stemmer teaches the DNA shuffling of the TEM-1 β-lactamase gene, a gene which catabolizes (i.e. hydrolyzes) the antibiotic cefotaxime.

Claim 4 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to detoxify a compound. Stemmer teaches a method of evolving the biocatalytic activity of a cell. Specifically, Stemmer teaches the DNA shuffling of the TEM-1 β-lactamase gene, a gene which catabolizes (i.e. detoxifies) the antibiotic cefotaxime.

Claim 5 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to synthesize a compound of interest. Stemmer teaches this embodiment wherein he teaches the DNA shuffling of the TEM-1 β-lactamase gene, a gene which synthesizes detoxified cefotaxime.

Claim 6 is drawn to an embodiment of Claim 4, wherein the compound is an antibiotic. Stemmer teaches this embodiment wherein Stemmer teaches the DNA shuffling of the TEM-1 β-lactamase gene, a gene which catabolizes (i.e. detoxifies) the antibiotic cefotaxime.

Claim 12 is drawn to an embodiment of Claim 1, wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the TEM-1 β-lactamase gene, a gene which

catabolizes (i.e. detoxifies) the antibiotic cefotaxime. In this reference Stemmer teaches performing at least one recombining step *in vitro* and that the resulting library is introduced into the cell (i.e. *E. coli*) whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated.

Claim 13 is drawn to an embodiment of Claim 12, wherein the *in vitro* recombining step comprises cleaving the first and second segments into fragments , mixing and denaturing said fragments followed by incubating said fragments with a polymerase under conditions wherein the denatured fragment will anneal and form a library of recombinant genes. Stemmer teaches this embodiment wherein Stemmer utilizes at least one recombining step comprises cleaving the first and second segments into fragments, mixing and denaturing said fragments followed by incubating said fragments with a polymerase under conditions wherein the denatured fragment will anneal and form a library of recombinants.

8. **Claims 1, 12, and 14-15** are rejected under 35 U.S.C. 102(e) as being anticipated by Khosla [US Patent no. 5,521,077 (filed 28 APR 94)].

Claim 1 is drawn to a method of evolving the biocatalytic activity of a cell comprising at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to catalyze a reaction of interest wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of enhancement is achieved.

Khosla et al. teach a method of evolving the biocatalytic activity of a cell. Specifically, Khosla et al. teach a method of generating multiple protein variants of DHFR i.e. evolving the biocatalytic activity of a cell, using a method comprising the steps recited in Claim 1. (see Examples 1-4).

Claim 12 is drawn to an embodiment of Claim 1, wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated.

Khosla et al. teach this embodiment wherein they teach the generation of DHFR mutants wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated.

Claim 14 is drawn to an embodiment of Claim 1, wherein at least one recombining step is performed *in vivo.* Khosla et al. teach this embodiment (see Examples 1-4 and Column 2, beginning at line 30).

Claim 15 is drawn to an embodiment of Claim 1, wherein the recombining step is performed in the cell whose biocatalytic function is to be enhanced. Khosla et al. teach this embodiment (see Examples 1-4 and Column 2, beginning at line 30).

9. **Claims 1-3, 5, 12-13, 17, 20-22, 25-26** are rejected under 35 U.S.C. 102(e) as being anticipated by Stemmer [US Patent no. 5,605,793 (filed 17 FEB 94 and published 25 FEB 97)].

Claim 1 is drawn to a method of evolving the biocatalytic activity of a cell comprising at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to catalyze a reaction of interest wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of enhancement is achieved. Stemmer teaches a method of evolving the biocatalytic activity of a cell.

Specifically, Stemmer teaches the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells using the steps recited in Claim 1.

Claim 2 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to utilize a substrate as a nutrient source. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells which utilize X-gal as a nutrient source.

Claim 3 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to catabolize a compound. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells which catabolize X-gal.

Claim 5 is drawn to an embodiment of Claim 1, wherein the reaction of interest is the ability to synthesize a compound of interest. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells which catabolize X-gal synthesizing a nondiffusable blue pigment (i.e. a compound of interest).

Claim 12 is drawn to an embodiment of Claim 1, wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells wherein at least one recombining step is performed *in vitro* and the resulting library is introduced into the cell (i.e. *E. coli*) whose biocatalytic activity is to be enhanced whereby a library of cells containing different recombinants is generated.

Claim 13 is drawn to an embodiment of Claim 12, wherein the *in vitro* recombining step comprises cleaving the first and second segments into fragments , mixing and denaturing said fragments followed by incubating said fragments with a polymerase under conditions wherein the denatured fragment will anneal and form a library of recombinant genes. Stemmer teaches this embodiment wherein they teach the DNA shuffling of the lacZα gene from LacZ$^-$ cells to produce LacZ$^+$ cells wherein the at least one recombining step comprises cleaving the first and second segments into fragments , mixing and denaturing said fragments followed by incubating said fragments with a polymerase under conditions wherein the denatured fragment will anneal and form a library of recombinant genes.

Claim 17 is drawn to a method of evolving a gene to have the ability to catalyze a reaction of interest. This method is to comprise at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to catalyze the reaction of interest wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments of step (a). This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to catalyze the reaction of interest relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of enhancement is achieved.

Stemmer teaches a method of evolving a gene to have the ability to catalyze a reaction of interest.. Specifically, Stemmer teaches the DNA shuffling of the lacZα gene (i.e $LacZ^-$ gene) to produce $LacZ^+$ cells using the steps recited in Claim 17.

Claim 20 is drawn to a method of optimizing the expression of a gene product . This method is to comprise at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from at least one gene conferring the ability to produce said gene product wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers optimized expression of said gene product relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers optimized expression of said gene product relative to the previously isolated recombinant gene. This method also comprises an optional step wherein steps © and (d) are repeated until the desired level of optimized expression is achieved.

Stemmer teaches a method of optimizing the expression of a gene product . Specifically, Stemmer teaches the DNA shuffling of the lacZα gene to produce $LacZ^+$ cells from $LacZ^-$ cells in a method comprising the steps recited in Claim 20. The expression can be said to be optimized because before

shuffling the cells produced inactive LacZ, however, after DNA shuffling the expression has been optimized because active LacZ could be produced.

Claim 21 is drawn to an embodiment of Claim 20, wherein the at least one gene encodes the gene product. Stemmer teaches this embodiment wherein he teaches the DNA shuffling of at least one gene (i.e. the lacZα gene) to produce $LacZ^+$ cells from $LacZ^-$ cells. The lacZα gene encodes the gene product LacZ.

Claim 22 is drawn to an embodiment of Claim 20, wherein the at least one gene is a vector comprising a gene encoding the gene product. Stemmer teaches this embodiment wherein he teaches the DNA shuffling of a mixture of two 2.7 kb whole plasmids each comprising inactive LacZ genes (See Example 2, Column 13) Following DNA shuffling and reassembly Stemmer teach that the expression of LacZ had been optimized i.e. $LacZ^+$ cells are present following transformation into *E. coli.*

Claim 25 is drawn to an embodiment of Claim 20, wherein the at least one gene is a host cell gene wherein the host cell gene does not encode the gene product. Stemmer teach this embodiment wherein he teaches that following DNA shuffling of the lacZα gene produces $LacZ^+$ cells from $LacZ^-$ cells in a method comprising the steps recited in Claim 25. The at least one gene is a host cell gene (i.e. the LacZα gene is a *E. coli* gene), however, the gene product is not expressed from the host cell gene but rather from the plasmid encoded gene.

Claim 26 is drawn to an embodiment of Claim 20, wherein optimization results in increased expression of the gene product. Stemmer teaches this embodiment wherein he teaches that following DNA shuffling of the lacZα gene $LacZ^+$ cells are produced from $LacZ^-$ cells in a method comprising the steps recited in Claim 26. The expression can be said to be increased because before shuffling the cells produced inactive LacZ, however, after DNA shuffling the expression was increased because active LacZ is produced.

35 U.S.C. § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

CLAIM REJECTIONS UNDER 35 USC § 103

12. **Claims 27-28 and 30** are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer [US Patent no. 5,605,793 (filed 17 FEB 94 and published 25 FEB 97)]as applied to Claims 1-3, 5, 12-13, 17, 20-22, 25-26 above and further in view of Ippoloto et al.(MAY 1995).

Claim 27 is drawn to a method of evolving a biosensor for a compound (compound A) of interest. This method is to comprise at least four steps. The first step of the method comprises the recombining of at least a first and a second DNA segment from a gene conferring the ability to detect a related compound (compound B) wherein a library of recombinant genes is produced. The first and second DNA segments must differ from each other in at least two nucleotides. Next, the library is screened for at least one recombinant gene that confers optimized ability to detect the compound of interest (compound A) relative to the wildtype form of the gene. The third step comprises recombing at least a segment of the recombined gene isolated in step (b) with a further DNA segment (i.e. a third DNA segment) from the gene being mutagenized. Said third fragment can be the same as or different from the first and second DNA segments. This third step is to result in a second library of recombinant genes. Finally, this second library is screened for at least one recombinant gene that confers enhanced ability to detect the compound of interest (compound A) relative to the previously isolated recombinant gene. This method also

comprises an optional step wherein steps © and (d) are repeated until the desired level of ability is achieved. Stemmer teaches a method of evolving a biosensor for a compound (compound A) of interest. Specifically, Stemmer teaches a method for evolving a gene such that the gene product has an enhanced capability of a particular ability. Stemmer does not teach using this methodology in combination with biosensors. However, Ippoloto et al. do teach mutagenizing carbonic anhydrase II (CAII) via oligonucleotide directed mutagenesis in order to increase the affinity of the protein for Zinc. Finally, the authors state that their structure-assisted design approach may be effective in the development of high sensitivity metal. ion biosensors. Therefore absent an unexpected result it would have been *prima facie* obvious to the skilled artisan at the time of the invention to use the Stemmer mutagenesis method in combination with the development of more sensitive biosensor assays. The skilled artisan would have been motivated to modify the teachings of Stemmer with those of Ippoloto et al. in order to rapidly and easily generate CAII mutants with improved binding affinity for zinc.

Claim 28 is drawn to an embodiment wherein optimization results in increase amplitude of response by the biosensor. Although the reference is silent as regards an increase amplitude of response by the biosensor. The skilled artisan would have reasonably expected such an improved response as Ippoloto et al. teach that one of the mutant that they produced had a 200-fold improvement in metal affinity.

Claim 30 is drawn to an embodiment wherein compounds A and B. Stemmer et al. in view of Ippoloto et al. teach this embodiment as argued above in the rejection of Claim 27.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102/103

13. **Claim 19** rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Short et al. [US Patent No. 5,958,751 (1999)].

Short et al. teach a modified form of a cell. Admittedly, Short et al. do not teach making the modified cell as set forth in the claim, however, it is well established that even though product-by-process claims are limited by and defined by the process, the determination of the patentability of the product is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re*

Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). Also, note that without defining in the claim what is meant by "recursive sequence recombination, it can be argued that Short et al. do teach a modified cell made by recursive sequence recombination. While the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

14. **Claim 19** rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Khosla et al. [US Patent No. 5,521,077 (1996)].

Khosla et al. teach a modified form of a cell. Admittedly, Khosla et al. do not teach making the modified cell as set forth in the claim, however, it is well established that even though product-by-process claims are limited by and defined by the process, the determination of the patentability of the product is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). Also, note that without defining in the claim what is meant by "recursive sequence recombination, it can be argued that Khosla et al. do teach a modified cell made by recursive sequence recombination. While the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

15. **Claim 19** rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen et al. [PNAS (1993)].

Chen et al. teach a modified form of a cell. Admittedly, Chen et al. do not teach making the modified cell as set forth in the claim, however, it is well established that even though product-by-process claims are limited by and defined by the process, the determination of the patentability of the product is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 227

USPQ 964, 966 (Fed. Cir. 1985). Also, note that without defining in the claim what is meant by "recursive sequence recombination, it can be argued that Chen et al. do teach a modified cell made by recursive sequence recombination. While the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

DOUBLE PATENTING

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. **Claims 1-18 and 20-30** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-36 of U.S. Patent No. 5,837,458. Although the conflicting claims are not identical, they are not patentably distinct.

18. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain

a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See Miller v. Eagle M.G. Co., 151 U.S. 186 (1894); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957). A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

19. **Claims 1-30** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-30 of copending Application No. 09/490,642. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

CONCLUSION

20. **Claim 1-30** are rejected or objected to for the reason(s) set forth above.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, PhD. whose telephone number is (703) 308-6567. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

The fax number for this Art Unit is (703) 308-8724. Before faxing any papers please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989). Any inquiry of a general nature or relating to the status of this application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Ethan Whisenant, Ph.D.
Patent Examiner (FSA)

Sample Statement

Sample Request to Use Computer Readable Form from Another Application

The following paragraph, or language having the same effect, can be used to invoke the procedures of 37 CFR section 1.821(e) in which an identical computer readable form from another application is used in a given application. The paragraph should be incorporated into a separate paper to be submitted in the given application.

> The computer readable form in this application 08/100,000, is identical with that filed in Application Number 07/999,999, filed March 1, 1988. In accordance with 37 CFR 1.821(e), please use the [first-filed, last-filed or only, whichever is applicable] computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is [included in the originally-filed specification of the instant application, included in a separately-filed preliminary amendment for incorporation into the specification, whichever is applicable]